EXHIBIT 2

IN THE UNITED STATES DISTRICT COURT
DISTRICT OF DELAWARE

NIPPON SHINYAKU CO., LTD., Plaintiff, **v.** **SAREPTA THERAPEUTICS, INC., Defendant.**	**C.A. No. 21-1015 (GBW)**
SAREPTA THERAPEUTICS, INC. and THE UNIVERSITY OF WESTERN AUSTRALIA, Defendant and Counter-Plaintiff **v.** **NIPPON SHINYAKU CO., LTD. and NS PHARMA, INC., Plaintiff and Counter-Defendants.**	

EXPERT REBUTTAL REPORT OF DR. MATTHEW J.A. WOOD

October 11, 2023

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Other relevant considerations include various prior art approaches employed in the art, types of problems encountered in the art, the rapidity with which innovations are made, and the sophistication of the technology involved.

10. I understand that NS and Sarepta have generally offered similar definitions of a POSA for the NS Patents. Dowdy Rpt. ¶¶ 19-20. For purposes of this report, I have applied Dr. Dowdy's definitions of a POSA for the NS Patents. However, if NS's definition were adopted, this does not affect my opinions.

IV. SCOPE AND CONTENT OF THE PRIOR ART AS OF AUGUST 2011

A. There Were No Recognized "Hot Spots" Within Exon 53 As of August 2011.

11. Dr. Dowdy opines that "by August 31, 2011, the hot spot within exon 53 had been identified and repeatedly verified." Dowdy Rpt. ¶ 110. I disagree. Dr. Dowdy arrives at this opinion by selectively reviewing the art and cherry-picking results to determine such a "hot spot." *Id.* ¶¶ 91-109. As I describe below, as of August 31, 2011, there was no recognized "hot spot" within exon 53 for targeting with an AON to induce skipping of exon 53. In my experience, "hot spots" are vanishingly rare, and to my knowledge do not exist within the human dystrophin gene. Thus, while I adopt Dr. Dowdy's term, I do not agree with the underlying premise that a "hot spot" within exon 53 in fact exists, much less was recognized in 2005 by Dr. Wilton or others.

1. State of the Art as of June 2005

12. As of 2005, there were only a few groups working to develop antisense oligonucleotides ("AONs") for treatment of Duchenne Muscular Dystrophy. Several research groups had joined consortiums based largely on geography – Netherlands/Belgium and United Kingdom – and there were also groups working in Japan. *See* Muntoni et al., Neuromuscular

6. Watanabe et al.: August 2011

64. Watanabe et al. filed PCT/JP2011/070318 on August 31, 2011 ("Watanabe PCT '318"). I understand the patents asserted by NS each claim priority to Watanabe PCT '318, and share a common specification. For convenience, I will cite to the specification of U.S. 10,647,741 ("the '741 patent"). I understand the inventors later published an article describing the work underlying Watanabe PCT '318. Watanabe et al., Mol Ther Nucleic Acids, 13:442-449 (2018) ("Watanabe 2018"). As Dr. Dowdy acknowledges, the inventors of Watanabe PCT '318 made and tested a series of overlapping 25 base AONs targeting the *entirety* of exon 53. '741 patent, Table 7 and Figs. 13-17; Watanabe 2018, at 443; Dowdy Rpt. ¶¶ 459-460. That the Watanabe PCT '318 inventors undertook the effort and cost of evaluating the entirety of exon 53 supports my opinion that the information known in the art at the time, including that disclosed in Wilton PCT '057, was insufficient to identify or define a "hot spot" within exon 53.

B. <u>Designing An AON That Would Induce Exon Skipping Was Unpredictable As of August 2011.</u>

1. There Were No Recognized "Hot Spots" as of August 2011.

65. Dr. Dowdy concludes that "by August 31, 2011, the hot spot within exon 53 had been identified and repeatedly verified." Dowdy Rpt. ¶ 110. I disagree—as described above, the conclusions that Dr. Dowdy drew from these publications were a misreading of the data as a whole. These laboratories use a variety of AON chemistries (e.g., 2'-O-methyl, PMOs, PPMOs, and ENAs) and divergent (or undisclosed) experimental parameters. Even the concept of a "hot spot" ignores the impact of length on an AON's ability to induce exon skipping, which is an important factor linked to the fundamental biophysical properties of the AON and its binding affinity, *e.g.,* how strongly it is likely to bind to the target sequence. Further, overarching

conclusions cannot be drawn from comparing these studies or in the field at all—as is well-known amongst those with more extensive experience with exon skipping studies, as illustrated by the articles discussed above.

66. Dr. Dowdy provides a summary of the AONs published as of August 31, 2011 in support of his conclusion. Dowdy Rpt. Fig. 18. In my opinion, Dr. Dowdy's Figure 18 is a classic example of confirmation bias. First, Dr. Dowdy selectively included only those AONs that overlap with the exon 53 region he believes was the "hot spot."

67. Second, Dr. Dowdy omits or ignores the information in the very same publications (and others) that show researchers designing and testing AONs outside of his putative "hot spot." For example, the Royal Holloway group reported on AONs both upstream and downstream of the "hot spot" (h53B1, h53B2, h53B3, h53C1, h53C2, h53C3, h53D1, h53D2, h53D3, h53D4, h53D5), as did Sarepta (SEQ ID Nos: 416, 418, 420, 422, 424, 426, 436, 436, 439, 440, 443, 444, 445, 446, 447, 448, 449, 450, 451 in Sazani '586), as did Wilton (H53A(-15+15), H53A(-32-06), H53A(-38-13). H53A(-49-26), Hint52(-47-23), H53A(+69+98) in Wilton PCT '350). Indeed, the majority of the AONs in each of the publications discussed above were outside of Dr. Dowdy's alleged "hot spot." If Wilton PCT '057 had identified a "hot spot" recognizable by other researchers, there would have been no need for NS, Popplewell or Sazani to screen the entirety of exon 53 in 2010, or for Wilton to make and test AONs outside of the "hot spot" in 2011.

68. Third, Figure 18 lacks nuance and important information. Dr. Dowdy failed to note the AONs that induce *little or no* exon skipping overlapping with his putative "hot spot." For example, the 2'-O-methyl versions of H53A(+23+47), H53A(+45+69) and H53A(+39+62) in Wilton PCT '057, h53A3 (+41+65), h53A5 (+47+71), h53A6 (+50+74), h53A30/5 (+42+72)

in Popplewell 2009, and the PPMO version of H53A(+39+69) in Sazani '586, all were reported to induce little or no skipping. Yet in Figure 18, Dr. Dowdy fails to distinguish between these AONs that had barely any detectable exon skipping (or yielded inconsistent results) and AONs that were reported to have greater activity. In my opinion, a POSA would take this additional information into account in designing AONs for exon 53 skipping or drawing any conclusions about the existence of a "hot spot."

69. In order to determine whether there are one or more "hot spot(s)" within exon 53 that, if targeted with an AON, would induce exon skipping, a full micro-walk of the exon would be necessary. Such a "micro-walk" would require an AON of a single length be moved base-by-base along exon 53. It would be important to understand which AONs induce exon skipping, but also to understand which AONs do not induce exon skipping. Moreover, it would be necessary to repeat this micro-walk for several AON lengths to account for the impact the length has on the ability of an AON to induce skipping. These studies had not been completed by August 2011, and to my knowledge have still not been published. Even if such micro-walk studies were completed, there may not be a discrete "hot spot" within exon 53 because as I note in my Opening Report, moving an AON by even a single base in the 5'- or 3'-direction can change its ability to induce exon skipping, sometimes very significantly.

2. Sequence Does Not Predict Exon-Skipping Activity

70. Dr. Dowdy opines that "a POSA would have reasonably expected "that ASOs complementary to the region of H53A(+30+65) "would successfully cause exon skipping." Dowdy Rpt. ¶ 418. I disagree. As I describe in my Opening Report, even today, one cannot predict *a priori* whether a given AON will induce exon skipping. Opening Report §§ IV.F-H; V.B-C. Dr. Wilton recognizes this, as he has repeatedly reported that the empirical studies are